

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**  
 (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32798A	<b>FOR FURTHER ACTION</b> <small>See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)</small>	
International application No. PCT/EP 03/14086	International filing date (day/month/year) 11.12.2003	Priority date (day/month/year) 12.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D409/04		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

- I  Basis of the opinion
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 11.06.2004	Date of completion of this report 28.02.2005
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Scruton-Evans, I Telephone No. +49 89 2399-8272

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No.

PCT/EP 03/14086

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-62 as originally filed

**Claims, Numbers**

9 (part), 10-16 as originally filed  
1-8, 9 (part) received on 16.02.2005 with letter of 16.02.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).  
*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,

claims Nos. 14

because:

the said international application, or the said claims Nos. 14 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

the written form has not been furnished or does not comply with the Standard.

the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N) Yes: Claims 1-16  
No: Claims

Inventive step (IS) Yes: Claims  
No: Claims 1-16

Industrial applicability (IA) Yes: Claims 1-13,15,16  
No: Claims

**2. Citations and explanations**

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents cited in the Search Report are referred to in this communication;

- D1: WO 03 040102 A (NOVARTIS PHARMA GMBH ;MANLEY PAUL WILLIAM (CH); NOVARTIS AG (CH);) 15 May 2003 (2003-05-15)
- D2: WO 03 040101 A (NOVARTIS PHARMA GMBH ;MANLEY PAUL WILLIAM (CH); NOVARTIS AG (CH);) 15 May 2003 (2003-05-15)
- D3: WO 2004 007458 A (AMGEN INC) 22 January 2004 (2004-01-22)
- D4: WO 2004 013102 A (SCHERING AG) 12 February 2004 (2004-02-12)
- D5: WO 02 090352 A (SCHERING AG ;ERNST ALEXANDER (DE); HABEREY MARTIN (DE); HUTH ANDRE) 14 November 2002 (2002-11-14)
- D6: WO 01 55114 A (NOVARTIS ERFIND VERWALT GMBH ;MANLEY PAUL WILLIAM (CH); NOVARTIS A) 2 August 2001 (2001-08-02) cited in the application
- D7: WO 00 27820 A (NOVARTIS ERFIND VERWALT GMBH ;HOFMANN FRANCESCO (CH); MANLEY PAUL) 18 May 2000 (2000-05-18) cited in the application
- D8: WO 02 066470 A (AMGEN INC) 29 August 2002 (2002-08-29)

Documents D1-D4 were all published after the priority or filing date of the present

application, and will thus not be taken into consideration in this written opinion.

With regard to the requirement for novelty (Article 33(2) of the PCT), D5 discloses compounds of the general formula I, which, when E is halogen, alkoxy, SR<sub>4</sub>, OR<sub>5</sub>, COOR<sub>8</sub> or CONR<sub>2</sub>R<sub>3</sub> overlap with the compounds of the present application. One intermediate compound, A-14a on page 65 has been excluded by means of a disclaimer but the general formula of the present application can be considered to represent a novel selection from D5 on the basis of the position of the group X and R<sub>2</sub>. D6 discloses compounds of the general formula I, the specific examples of which have been disclaimed by the first proviso in the present application. The general formula of the present application can be considered to represent a novel selection from that of D6 on the basis of the position of the X and R<sub>2</sub> groups. D7 discloses compounds of the general formula I, which overlap with the compounds of the present application. The 5th last compound on page 23 is excluded by the additional proviso in the present application. The general formula of the present application can be considered to represent a novel selection from D7, pages 21/22 on the basis of the position of the X and R<sub>2</sub> groups. D8 discloses compounds of the general formula I, which overlaps with the present application formula, and more specifically, claim 17. However, the compounds of the present application represent a novel selection from those disclosed in D8 on the basis of the position of the groups X and R<sub>2</sub>. In conclusion therefore, claims 1-16 satisfy the requirements of Article 33(2) of the PCT.

With regard to the requirement for inventive step (Article 33(3) of the PCT), the compounds of the present application are described as being inhibitors of angiogenesis and/or of the VEGF receptor tyrosine kinase. All of the prior arts D5-D8 disclose the same qualitative activity, and the man skilled in the art, faced with the problem of providing further novel compounds with this activity would have prepared the compounds of the present application, representing as they do a selection from those already known in the prior art, expecting them to have the same qualitative activity. Thus the problem is to be seen as the provision of compounds with unexpected advantages re the prior art, and in the absence of any evidence of such advantages, Article 33(3) of the PCT cannot be considered to have been satisfied. The expressions "substituted", "heteroaryl" etc further give rise to such a wide variety of compounds that any unexpected advantages shown must be such that it is reasonable to conclude that the claim represents a justified extrapolation of such advantages.

For the assessment of the present claim 14 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/14086

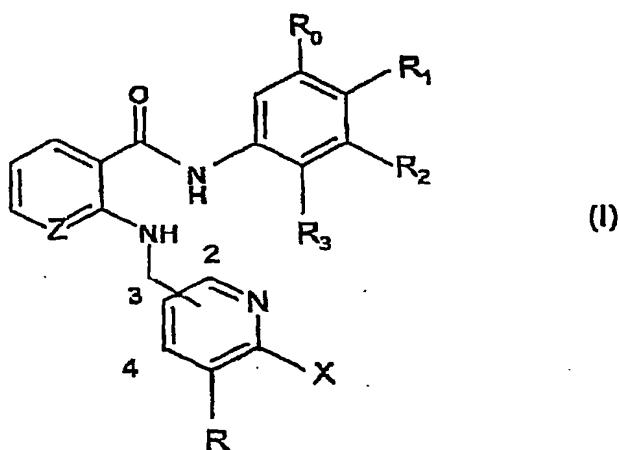
also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4-32798A

- 63 -

Claims:

1. An anthranilic acid amide of formula I,



wherein

R and R<sub>0</sub> represent H, halogen,

alkynyl, alkenyl, alkyl, which in each case is unsubstituted or substituted by halogen; unsubstituted or substituted mono- or bicyclic aryl; unsubstituted or substituted mono- or bicyclic heteroaryl having 1 to 3 heteroatoms selected from O, N or S; unsubstituted or substituted heterocycll having at least one N atom; mono- or dialkyl amino, wherein the alkyl radical is unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted mono- or bicyclic heteroaryl having 1 to 3 heteroatoms selected from O, N or S or substituted by unsubstituted or substituted heterocycll having at least one N atom; unsubstituted or substituted heterocycll carbonyl alkyl amino, wherein the heterocycll radical comprises at least one N atom;

R<sub>1</sub> represents H, halogen, unsubstituted or substituted C<sub>1-7</sub>alkyl, C<sub>2-7</sub>alkenyl, C<sub>2-7</sub>alkynyl, alkoxy or a radical

-O-(CH<sub>2</sub>)<sub>n</sub>-CF<sub>3</sub>, wherein n is 0, 1, 2 or 3,

R<sub>2</sub> is perfluoro alkyl,

R<sub>3</sub> represents H or halogen,

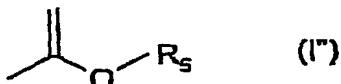
X represents hydroxy, alkoxy, alkyl thio, imino, alkyl imino, halogen, a radical of formula I'

4-32798A

- 64 -



wherein G is CH<sub>2</sub> or NH and R<sub>4</sub> is hydrogen, alkyl or aryl, or a radical of formula I"



wherein R<sub>5</sub> is alkyl or aryl,

Z is N or CH, and

wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 2-, 3-, 4- or 5-position,

under the proviso that R cannot represent H, if Z is nitrogen, X is hydroxy or methoxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position, R<sub>1</sub> and R<sub>3</sub> cannot both represent H if Z is CH, R represents H, X is hydroxy, alkoxy or alkyl thio and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position, and R<sub>1</sub> and R<sub>3</sub> cannot both represent H if Z is CH, R and R<sub>2</sub> both represent H, R<sub>2</sub> represents trifluoromethyl, X is bromo or hydroxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 4-position,

or an N-oxide or a tautomer thereof,

or a salt of such anthranilic acid amide, its N-oxide or its tautomer.

## 2. An anthranilic acid amide of formula I according to claim 1, wherein

R represents H, halogen,

alkynyl, alkenyl, alkyl, which in each case is unsubstituted or substituted by halogen;

unsubstituted or substituted mono- or bicyclic aryl;

unsubstituted or substituted mono- or bicyclic heteroaryl having 1 to 3 heteroatoms selected from O, N or S;

unsubstituted or substituted heterocycl having at least one N atom;

mono- or dialkyl amino, wherein the alkyl radical is unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted mono- or bicyclic heteroaryl

4-32798A

- 65 -

having 1 to 3 heteroatoms selected from O, N or S or substituted by unsubstituted or substituted heterocyclyl having at least one N atom;  
 unsubstituted or substituted heterocyclyl carbonyl alkyl amino, wherein the heterocyclyl radical comprises at least one N atom;

$R_0$  represents H,

$R_1$  represents H, halogen,  $C_{2-7}$ alkyl,  $C_{2-7}$ alkenyl,  $C_{2-7}$ alkynyl, alkoxy or a radical  $-O-(CH_2)_n-CF_3$ , wherein n is 0, 1, 2 or 3,

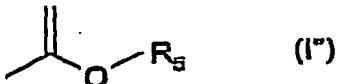
$R_2$  is perfluoro alkyl,

$R_3$  represents H or halogen,

X represents hydroxy, alkoxy, alkyl thio, imino, alkyl imino, halogen, a radical of formula I'



wherein G is  $CH_2$  or NH and  $R_4$  is hydrogen, alkyl or aryl, or a radical of formula I''



wherein  $R_5$  is alkyl or aryl,

Z is N or CH, and

wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 2-, 3-, 4- or 5-position,

under the proviso that R cannot represent H, if Z is nitrogen, X is hydroxy or methoxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position,  $R_1$  and  $R_3$  cannot both represent H if Z is CH, R represents H, X is hydroxy, alkoxy or alkyl thio and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position,  $R_1$  and  $R_3$  cannot both represent H if Z is CH, R represents H,  $R_2$  represents trifluoromethyl, X is bromo or hydroxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 4-position,

or an N-oxide or a tautomer thereof,

or a salt of such anthranilic acid amide, its N-oxide or its tautomer.

## 3. An anthranilic acid amide of formula I according to claim 1

wherein

R represents H, halogen, alkenyl, alkyl, pyridyl alkyl amino, morpholinyl alkyl amino, alkyl piperazinyl alkyl amino, alkyl piperazinyl carbonyl alkyl amino, phenyl alkyl amino, alkyl amino, thienyl, pyridyl, furanyl, thiazolyl, naphthyl or phenyl which is unsubstituted or substituted by trifluoromethyl, phenyl, alkanoyl or alkanoyl amino,

R<sub>1</sub> represents H, halogen, C<sub>2-7</sub>alkyl, C<sub>2-7</sub>alkenyl, C<sub>2-7</sub>alkynyl, alkoxy or a radical -O-(CH<sub>2</sub>)<sub>n</sub>-CF<sub>3</sub>, wherein n is 0, 1, 2 or 3,

R<sub>2</sub> is perfluoro alkyl,

R<sub>3</sub> represents H or halogen,

X represents hydroxy, alkoxy, alkyl thio, imino, alkyl imino, halogen, a radical of formula I' wherein G is CH<sub>2</sub> or NH and R<sub>4</sub> is hydrogen or alkyl, or a radical of formula I"

wherein R<sub>5</sub> is alkyl,

Z is N or CH, and

wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 2-, 3-, 4- or 5-position,

under the proviso that R cannot represent H, if Z is nitrogen, X is hydroxy or methoxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position, R<sub>1</sub> and R<sub>3</sub> cannot both represent H if Z is CH, R represents H, X is hydroxy, alkoxy or alkyl thio and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position, R<sub>1</sub> and R<sub>3</sub> cannot both represent H if Z is CH, R and R<sub>0</sub> both represent H, R<sub>2</sub> represents trifluoromethyl, X is bromo or hydroxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 4-position,

or an N-oxide or a tautomer thereof,

or a salt of such anthranilic acid amide, its N-oxide or its tautomer.

## 4. An anthranilic acid amide of formula I according to claim 1, wherein

R represents H, halogen, lower alkenyl, lower alkyl, pyridyl lower alkyl amino, morpholinyl lower alkyl amino, lower alkyl piperazinyl lower alkyl amino, lower alkyl piperazinyl carbonyl lower alkyl amino, phenyl lower alkyl amino, lower alkyl amino, thienyl, pyridyl, furanyl, thiazolyl, naphthyl or phenyl which is unsubstituted or substituted by trifluoromethyl, phenyl, lower alkanoyl or lower alkanoyl amino.

$R_1$  represents H, halogen,  $C_{2-7}$ alkyl,  $C_{2-7}$ alkenyl,  $C_{2-7}$ alkynyl, lower alkoxy or a radical  $-O-(CH_2)_n-CF_3$ , wherein n is 0, 1, 2 or 3,

$R_2$  is trifluoromethyl,

$R_3$  represents H or halogen,

$X$  represents hydroxy, lower alkoxy, lower alkyl thio, imino, lower alkyl imino, halogen, a radical of formula I' wherein G is  $CH_2$  or NH and  $R_4$  is hydrogen or lower alkyl, or a radical of formula I" wherein  $R_5$  is lower alkyl.

$Z$  is N or CH, and

wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 2-, 3-, 4- or 5-position,

under the proviso that  $R$  cannot represent H, if  $Z$  is nitrogen,  $X$  is hydroxy or methoxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position,  $R_1$  and  $R_3$  cannot both represent H if  $Z$  is CH,  $R$  represents H,  $X$  is hydroxy, lower alkoxy or lower alkyl thio and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position,  $R_1$  and  $R_3$  cannot both represent H if  $Z$  is CH,  $R$  and  $R_6$  both represent H,  $X$  is bromo or hydroxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 4-position,

or an N-oxide or a tautomer thereof,

or a salt of such anthranilic acid amide, its N-oxide or its tautomer.

##### 5. An anthranilic acid amide of formula I according to claim 1, wherein

$R$  represents H, halogen, lower alkenyl, lower alkyl, pyridyl lower alkyl amino, morpholinyl lower alkyl amino, lower alkyl piperazinyl lower alkyl amino, lower alkyl piperazinyl carbonyl lower alkyl amino, phenyl lower alkyl amino, lower alkyl amino, thienyl, pyridyl, furanyl, thiazolyl, naphthyl or phenyl which is unsubstituted or substituted by trifluoromethyl, phenyl, lower alkanoyl or lower alkanoyl amino,

$R_1$  represents H, halogen,  $C_{2-7}$ alkyl,  $C_{2-7}$ alkenyl,  $C_{2-7}$ alkynyl, lower alkoxy or a radical  $-O-(CH_2)_n-CF_3$ , wherein n is 0 or 1,

$R_2$  is trifluoromethyl,

$R_3$  represents H or halogen,

$X$  represents hydroxy, lower alkoxy, halogen,

a radical of formula I' wherein  $R_4$  is hydrogen or lower alkyl, or

a radical of formula I" wherein  $R_5$  is lower alkyl,

-- 68 --

Z is N or CH, and

wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3- or 4-position,

under the proviso that R cannot represent H, if Z is nitrogen, X is hydroxy or methoxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position, R<sub>1</sub> and R<sub>3</sub> cannot both represent H if Z is CH, R represents H, X is hydroxy, lower alkoxy or lower alkyl thio and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position, R<sub>1</sub> and R<sub>3</sub> cannot both represent H if Z is CH, R and R<sub>3</sub> both represent H, X is bromo or hydroxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 4-position,

or an N-oxide or a tautomer thereof,

or a salt of such anthranilic acid amide, its N-oxide or its tautomer.

6. An anthranilic acid amide of formula I according to claim 1, wherein

R represents H, halogen, lower alkenyl, lower alkyl, pyridyl lower alkyl amino, morpholinyl lower alkyl amino, lower alkyl piperazinyl lower alkyl amino, lower alkyl piperazinyl carbonyl lower alkyl amino, phenyl lower alkyl amino, lower alkyl amino, thienyl, pyridyl, furanyl, thiazolyl, naphthyl or phenyl which is unsubstituted or substituted by trifluoromethyl, phenyl, lower alkanoyl or lower alkanoyl amino,

R<sub>1</sub> represents H, halogen, C<sub>2</sub>-alkyl, or C<sub>2</sub>-alkynyl,

R<sub>2</sub> is trifluoromethyl,

R<sub>3</sub> represents H or halogen,

X represents hydroxy, lower alkoxy, halogen,

a radical of formula I' wherein R<sub>4</sub> is hydrogen or lower alkyl, or

a radical of formula I" wherein R<sub>5</sub> is lower alkyl,

Z is CH, and

wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3- or 4-position,

under the proviso that R<sub>1</sub> and R<sub>3</sub> cannot both represent H in compounds of formula I wherein R represents H, X is hydroxy, lower alkoxy or lower alkyl thio and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position, R<sub>1</sub> and R<sub>3</sub> cannot both represent H if R and R<sub>3</sub> both represent H, X is bromo or

4-32798A

- 69 -

hydroxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 4-position,  
or an N-oxide or a tautomer thereof,  
or a salt of such anthranilic acid amide, its N-oxide or its tautomer.

7. An anthranilic acid amide of formula I according to claim 1, wherein  
R represents H, halogen, allyl, 3-methyl-buten-2-yl, propyl, ethylamino, pyridylethylamino, morpholinylethylamino, N-methyl-piperazinylpropylamino, N-methyl-piperazinylethylamino, N-methyl-piperazinylacetylamino, benzylamino, thienyl, pyridyl, furanyl, thiazolyl, naphthyl or phenyl which is unsubstituted or substituted by trifluoromethyl, phenyl, formyl or acetylamino,

R<sub>1</sub> represents H, halogen, propyl, propynyl,

R<sub>2</sub> is trifluoromethyl,

R<sub>3</sub> represents H or halogen,

X represents hydroxy, lower alkoxy, halogen,

a radical of formula I' wherein R<sub>4</sub> is hydrogen or lower alkyl, or

a radical of formula I" wherein R<sub>5</sub> is lower alkyl,

Z is CH, and

wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3- or 4-position,

under the proviso that R<sub>1</sub> and R<sub>3</sub> cannot both represent H in compounds of formula I wherein  
R represents H, X is hydroxy, lower alkoxy or lower alkyl thio and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3-position, R<sub>1</sub> and R<sub>3</sub> cannot both represent H if R and R<sub>5</sub> both represent H, X is bromo or hydroxy and wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 4-position,

or an N-oxide or a tautomer thereof,

or a salt of such anthranilic acid amide, its N-oxide or its tautomer.

8. An anthranilic acid amide of formula I according to claim 1, wherein

R represents halogen, lower alkenyl, lower alkyl, pyridyl lower alkyl amino, morpholinyl lower alkyl amino, lower alkyl piperazinyl lower alkyl amino, lower alkyl piperazinyl carbonyl lower alkyl amino, phenyl lower alkyl amino, lower alkyl amino, thienyl, pyridyl, furanyl,

4-32798A

- 69a -

thiazolyl, naphthyl or phenyl which is unsubstituted or substituted by trifluoromethyl, phenyl, lower alkanoyl or lower alkanoyl amino.

R<sub>1</sub> represents H,

R<sub>2</sub> is trifluoromethyl,

R<sub>3</sub> represents H,

X represents hydroxy or lower alkoxy,

Z is CH, and

wherein the methylen group is attached to the pyridyl moiety at the carbon atom of the pyridyl moiety in 3- or 4-position,

or an N-oxide or a tautomer thereof,

or a salt of such anthranilic acid amide, its N-oxide or its tautomer.

9. An anthranilic acid amide of formula I according to claim 1 selected from

2-[(6-Methoxy-3-pyridinyl)methyl]amino-N-[4-bromo-3-(trifluoromethyl)phenyl]benzamide,

2-[(2-Bromo-4-pyridinyl)methyl]amino-N-[(3-trifluoromethyl)phenyl]benzamide,

2-[(6-Methoxy-4-pyridinyl)methyl]amino-N-[3-(trifluoromethyl)phenyl]benzamide,

2-[(6-Methoxy-3-pyridinyl)methyl]amino-N-[2-fluoro-3-(trifluoromethyl)phenyl]benzamide,

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